ETHICS

Uncomfortable implications: placebo equivalence in drug management of a functional illness

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Using a fictional but representative general practice consultation, involving the diagnosis of irritable bowel syndrome in a patient who is anxious for some relief from the discomfort his condition entails, this paper argues that when *both* (a) a drug fails to out-perform placebo *and* (b) the condition in question is a functional illness with no demonstrable underlying pathology, *then* the action of the drug is not only no better than placebo, and it is also no different from it either. The paper also argues that, in the circumstances of the consultation described, it is striking that current governance deems it ethical for a practitioner to prescribe either a drug or a placebo, both of which appear to rely for their effectiveness on a measure of concealment on the part of the doctor, yet deems it unethical for a practitioner openly to prescribe a harmless and enjoyable substance which (in equivalent conditions of transparency and information) is likely to be no less effective than either drug or placebo and is also likely to be better-tolerated and cheaper than the drug.

We here describe a fictitious consultation between a patient, Mr Smith, and his general practitioner, Dr Jones, concerning a condition commonly presented to general practice consultations, together with characteristic and, we think, philosophically curious features of the management of this condition by drugs.

Mr Smith visits Dr Jones with vaguely disordered digestion, including urgency, inconsistency and irregularity of bowel movements coupled with mild abdominal pain, discomfort and bloating. After various tests have ruled out organic disease, Dr Jones concludes that the best, or only available, label for Smith's problem is irritable bowel syndrome (IBS) and considers what help she might be able to offer Smith for this problem. (Up to a third of the patients in whom she diagnoses gastrointestinal disorders in her surgery receive the specific diagnosis of IBS.[1])

Dr Jones explains to Smith that ''SAS'' is a specific antispasmodic that has been developed for use with people who have IBS but that clinical trials are inconclusive with regard to the relative extent to which it benefits the patients treated. Previous enthusiasm[2] for antispasmodics has more recently been called into question.[3] A typical estimate might be that antispasmodics would be found helpful by about 35% of people with IBS. The other 65%, of course, were not particularly helped by it, so Smith's basis for accepting this treatment would be the prospect of a roughly one-in-three chance of benefit. The symptoms of his particular form of IBS are sufficiently disliked by Smith for him to welcome this chance of relief.

Dr Jones and Mr Smith know one another well, and Dr Jones wishes Smith to make as informed and sophisticated a decision as possible, so she explains the complexities and uncertainties of the treatment decision as she sees them. In particular, the information about the effectiveness of SAS was obtained from a large trial comparing it with placebo, and in fact the proportion of people who experienced relief from symptoms while taking only the placebo was practically the same as the proportion of people helped by SAS—about 35% in that particular trial (although placebo has sometimes appeared to outperform this significantly, offering seeming benefit to up to 70% of patients in some trials, with the perceived benefits lasting for a year or more[4]).

Initially Smith is somewhat put off by this disclosure, but he pursues the matter in conversation with Dr Jones, as follows. He reasons that the two proportions of people obtaining benefit—35% of their respective study populations in each case—may be importantly distinct. The beneficiaries of SAS may be responding to the real action of a real drug, whereas the beneficiaries of placebo may be responding to the power of suggestion alone, or they may simply be recovering spontaneously. As Smith puts it to Dr Jones, we know how the active drug *can* work (the notion of ''work'' is undefined), so it is reasonable to suppose that, when it does work, this is how an objective improvement is achieved. By contrast, we know that the inactive placebo *cannot* work (similarly undefined), so it is reasonable to suppose that those who benefit from it do so only subjectively, imagining the improvement or obtaining it from the encouragement afforded by beliefs that are ultimately mistaken.

Dr Jones' scruples oblige her to rebut this suggestion. She explains that in her view there is no real basis on which to make the distinction between the two sources of benefit for the two 35% subgroups. The reason is this. With a functional illness, that is, an illness that is essentially constituted by the symptoms and that lacks discernible underlying disease processes, there simply is no objective improvement that can be demonstrated, other than the relief of symptoms. This follows straightforwardly from the fact that, at least at our current state of knowledge,[5] there is

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Abbreviations: IBS, irritable bowel syndrome; SAS, [hypothetical] specific antispasmodic

nothing identifiably wrong (in the pathophysiological sense) in the first place, apart from the symptoms themselves: the disorder is identified and defined solely in terms of what the patient reports (p 1480).[6] This is emphatically not to deny the reality of the symptoms. Quite apart from the subjective discomfort experienced by the patient, the pattern and nature of bowel movements are all-too-demonstrable. Moreover, in identifying IBS as a functional illness, Dr Jones is most certainly not asserting those symptoms to be imagined, or fabricated, or to result from aberrant psychology. The term ''functional illness'' is here used descriptively, not evaluatively (whether pejorative or otherwise).[7] The description refers simply to the fact of evident symptoms arising from no discernible underlying disease processes, a phenomenon with a significant and increasing incidence in general practice consultations.[8] (Nor is Dr Jones dismissing as irrelevant the question of what triggers a response in the minority of patients whose condition does improve. On the contrary, the question is an intriguing one, and it inevitably draws our attention to the weight of psychological or social factors in the complex of factors which lies behind typical presentations of IBS.)

A logical consequence of this is, however, that one person's experience of symptoms is liable to be as compelling as another's, and more particularly one person's subjective relief of symptoms is as good as any other person's: it does not matter whether the relief follows the taking of an ''active'' specific drug such as SAS or placebo.

Furthermore, argues Dr Jones, we have therefore no real way of knowing whether people who get symptomatic relief following the use of SAS are getting it by any means other than precisely those unexplained processes that underlie symptomatic relief after the taking of placebo.

This indicates to Mr Smith that in fact he has almost no basis for choosing between the ''active'' SAS and the inactive placebo. Almost none, but not quite: for, it occurs to him, he could not meaningfully choose placebo without knowing precisely what it was. And then, he reasons, it could not work—assuming that the power of placebo relies on his suggestibility, which, in turn, relies on his ignorance of its real nature. On this assumption, then, the unblinding of placebo does give him an objective basis for choosing SAS.

Dr Jones agrees that she has in this sense unblinded placebo, but points out that in effect she has unblinded SAS as well, by acknowledging its therapeutic equivalence to placebo. Thanks to this scrupulous explanation, Smith now knows that SAS is no better than placebo.[i] Worse, he now knows also that, with an essentially symptomatic condition such as his irritable bowel syndrome, symptom relief is the only criterion of success. Therefore, the effectiveness of SAS is no better than that of placebo, and we have no grounds for believing it to be any different from it, either.

This initially surprising conclusion follows from the fact that there are (as yet; but see Talley and Spiller[5]) no discernible underlying faulty processes that are in any sense fixed or mended by the action of the drug. Of course *something* is ''faulty''—unwanted or aberrant—concerning Smith's digestive system, either at the level of its function or in the way that Smith notices or perceives what is going on within him. In so far as this were eased or, perhaps, made less apparent to Smith, following the doctor's intervention, then we could speak (somewhat loosely) of its being ''remedied''. But this is to say rather less than might at first appear.

First, a real change in the behaviour of Smith's gut might indeed take place—but in the absence of a demonstrable reversal of pathology, it must remain precisely that change which would necessarily take place in the process of symptom relief from whatever cause, including placebo. Alternatively, if, instead of his gut's actual behaviour, what changed were simply Smith's faulty *perception* of motility in his gut (whereby normal motility felt uncomfortable and often painful, in the way that actual spasm would), then of course there was no spasm to be fixed: antispasmodics were doing precisely nothing *as antispasmodics*, other than functioning as a placebo!

Dr Jones presses home the point. Mr Smith's grounds for initially preferring to take SAS (ie, an assumed causal action at some level of underlying disease) must now give way to the merely empirical grounds for faith in the drug, namely a roughly one-in-three chance of finding himself among those people whom clinical trials have shown to obtain relief from taking SAS.[ii] It is not merely that these grounds are no better than the grounds for faith in the placebo. The point is that they are actually the same grounds—namely, the available results, showing Mr Smith to have about a one-in-three chance of being helped whether he takes SAS or placebo.

Smith remains uneasy. At the back of his mind is the sceptical thought that the therapeutic equivalence of SAS and placebo emerged from trials in which placebo must presumably have played its ordinary role, that is, in disguise. He, on the other hand, has had the benefit of a thoughtful explanation from his doctor, whose scruples extended to the unblinding of the placebo. The patients in the trial did not have that explanation, nor did they know what preparation they were taking at any particular time—the trial required precisely such ''blinding'' on the part of patients and clinical investigators alike. Thus, armed with knowledge that they did not have, Smith is forever set apart from the patients in the trial. If his being helped by a doctor's prescription depends on his faith in the product, those chances now seem to have fallen—both for placebo and for SAS—by their unblinding at the hand of Dr Jones. This conclusion seems to Smith both disappointing and somehow slightly suspect, but he cannot put his finger on the difficulty right away and makes a mental note to come back to it. Meanwhile, Dr Jones is doing something surprising.

Taking a packet of well-known proprietary chocolate sweets—let us call them Swotties—she carefully counts out all those with a green candied coating, and puts them on the desk in front of Mr Smith. Having previously established that Smith has no intolerance of either sugar or chocolate, Jones observes that from the pharmacological point of view regarding Smith's digestive tract, the green chocolate drops are just as inactive as conventional placebos, themselves inert sugar pills. She now suggests prescribing green Swotties instead of either SAS or the ''official'' placebo. Since Swotties *are* inactive in the relevant sense, and are pharmacologically comparable to placebo, we have no prior reason for believing them to function either more or less effectively than the placebo. We should therefore expect a roughly one-in-three chance that Smith would obtain symptomatic relief by taking them, *if* he did so ''blindly'' as would have been the case with SAS and placebo in the original trial. As we know, this 35% response is in turn as effective as the response to SAS. There is therefore no reason to

[i] When both are blinded. We are unaware of any trials comparing them when both are unblinded as we define that term here in relation to SAS and placebo. Such a trial would compare an open-label placebo with open-label SAS, the participants knowing both what preparation they were receiving and also the fact of the placebo-equivalence of SAS, which was presumably not known to the participants in the original trial. An alternative suggestion, which we owe to Dr Michael King, would be for an open-label placebo to be trialled against an open-label drug acknowledged as being only problematically relevant (cf trials of various cardioactive drugs thought to have therapeutic potential for the management of Alzheimer disease, for example).

[ii] We are grateful to Dr Martin Schlup for this point.

expect a difference in effectiveness between SAS and Swotties, were both to be blinded.

There are, however, differences in other respects. Swotties are more palatable than placebo, and significantly more palatable than SAS. They are substantially cheaper than SAS. Furthermore, so far as we know, people who are tolerant of sugar and chocolate will incur none of the (admittedly rare) side-effects associated with SAS.

The most significant difference from the point of view of the clinical consultation is, however, in the societal rather than the physiological realm: Dr Jones has no authority to prescribe Swotties. As a registered medical practitioner, regulated (in the UK) by the General Medical Council, Dr Jones has authority to prescribe licensed drugs, and in certain circumstances to permit her patients to receive ''official'' placebos (for instance in the course of an approved clinical trial procedure). She even has tacit authority to prescribe a medicine that she believes to be specifically ineffective, albeit harmless, in an individual case, if for instance this is done in the sincere expectation that the larger ritual of prescription and taking of a medicine will be of help to the patient. In such cases an otherwise active drug is in effect serving as a placebo, or is contributing to the placebo effect of the consultation and prescription as a whole. This authority to prescribe becomes manifestly problematic and irregular if extended to Swotties, for the following reasons.

In the case of prescribing licensed drugs, the medical practitioner's competence concerns the physiological and pharmacological understanding of when and why drugs may be needed clinically, how and why they offer benefit, how and why they may pose the risk of harms, how such harms are to be evaluated in the context of hoped-for clinical benefit and how any such harms are to be managed and mitigated should they occur. This general expertise also extends to the understanding of, and competent authority to prescribe, drugs which are only presumptively effective, and indeed drugs that are possibly ineffective, inasmuch as their general impact upon the patient is a matter for the doctor's legitimate judgement and recommendation. Thus, in the specific case of SAS, if it had turned out to work more reliably than placebo, Dr Jones would have the sort of specialist knowledge normally called upon to explain and exploit that working.

In the case of prescribing placebo, she is on less-safe but still tolerable ground. ''Official'' placebos, though inactive, have been safely prepared in a controlled pharmaceutical laboratory, ordinarily have no side effects and hold an acknowledged place in the methods of the medical profession historically and in the contemporary conduct of clinical research.

In the case of Swotties, none of these conditions is met. Even though Swotties are likely to be no less effective than SAS, are demonstrably cheaper, self-evidently more enjoyable and almost certainly safer, they are not licensed for medicinal use and they have no recognised medicinal properties.

This is the official position, but Dr Jones admits to some dissatisfaction with it, and proceeds to explore this dissatisfaction. As she points out, Mr Smith's attitude towards the antispasmodic SAS was one of initial enthusiasm for the one-in-three chance of benefit that it offered, followed by the cooling of his enthusiasm upon being told that its performance in clinical trials was no better than that of placebo. It seems to follow that Smith's faith in SAS, and hence his suggestibility regarding its benefits, relied on Dr Jones' withholding the information about its placebo-equivalence. She could, therefore, have prescribed SAS most effectively only if she had concealed the placebo-equivalence.

This seems straightforwardly comparable with the lack of transparency that is generally supposed to underlie successful use of placebo—namely, to enjoy the benefits of the power of suggestion, it seems that the doctor must conceal from the patient at least some of the pertinent facts about the substance prescribed. Dr Jones' point is that this seems inescapably true of actual placebos and of supposedly ''active'' drugs as well, *if* (a) their performance is placebo-equivalent *and if* (b) in such functional conditions as irritable bowel syndrome, there is no demonstrable action to which the symptomatic improvement can be specifically and demonstrably attributed. (It will be recalled that this follows logically from there being no discernible underlying defect in need of repair.)

Therefore, in prescribing either an ''official'' placebo or SAS, Dr Jones would ordinarily expect even the limited (35%) hope of success to rest on her concealing from Smith some of the pertinent facts. Were she ethically unhappy about this concealment—and she is deeply unhappy—then she is to that extent inhibited from prescribing either. In a nutshell, her question is this: how can it be morally acceptable to conceal the truth about the efficacy of SAS or placebo, when at the same time it is thought morally unacceptable to prescribe Swotties transparently? Answers couched in terms of professional authority seem to miss the point or to beg the question.

Mr Smith now takes the opportunity to recall and articulate his unsatisfying interim conclusion, namely that with both SAS and placebo unblinded, he can no longer hope to find himself among the 35% of either those receiving the drug or those receiving the dummy.[iii] He now proposes that this disappointing thought can be evaded, as follows.

Smith conjectures that the damage done by unblinding need not be the same in the two cases. When the effectiveness of SAS compared with placebo was unblinded, it seemed to him initially as though he had lost all faith in it in just exactly the same way as he would lose faith in placebo upon its being unblinded. But now he is not so sure.

The unblinding of placebo means declaring it to be the pharmacologically inactive substance that it really is. This entails that all pretence to any kind of causal action on Smith's digestive system be given up. That pretence *was* ''the mask''. Leaving aside spontaneous remission, the only thing left to the patient in this circumstance is a state of faith, together with whatever powers of the mind this engenders over the truculent digestive tract. But once the pretence, and with it ''the mask'', is taken away, the benefits of faith arising specifically from the placebo are thereby taken away also.

By contrast—reasons Smith—the unblinding of SAS is not like this. He need not give up all pretence of there being some kind of causal action on his digestive system. On the contrary, he presumes, there is a substantial body of literature detailing how specific antispasmodic products *might* act upon his gut. Even if only one digestive tract in three is actually helped in this

[iii] We accept that a drawback of placebo controlled trials is their inability to distinguish between individual patients who might have benefited from the intervention—that is, real people, rather than ''statistical people'' who might have experienced an effect somewhere in the trial population. However, our interpretation of trials is based on the overall interpretation of results; an ''effect'' calculated overall to be around that of placebo is not interpreted positively. Clinical practice eschews the use of interventions with such results in the absence of other reasons to think the intervention worthwhile in an individual case. Basing clinical practice on a chance, literally, that the patient will receive benefit greater than placebo defies the tenets of evidence based practice, particularly as active drugs frequently have side effects. It may be that certain subgroups of patients could be identified who might have unequivocal benefits from the intervention, but establishing this would require new trials.

[iv] If eaten and enjoyed as intended, Swotties cannot be blinded. Blinding them—for instance, by requiring that they be swallowed whole rather than chewed—entails losing their advantage in palatability, but their other advantages remain.

way, at least—reasons Smith—such help indicates an explainable effect that does not simply collapse into blind faith.

Not so, responds Dr Jones, laying out the full implication of her earlier point about the actions of both drug and placebo. Without either (a) a measurable difference in the effectiveness of SAS compared with placebo (ie, a difference in need of explanation) or (b) a demonstrable underlying disease process that doesn't consist solely of the symptoms Smith experiences (ie, a source of explanation, had one been needed), we simply have no grounds for distinguishing one set of improved digestive behaviours from another. We can distinguish no phenomena—nothing at all—that can plausibly be attributed to the specific action of the antispasmodic drug, as distinct from the specific action of the patient's suggestible conscious or unconscious mind, or the unconnected spontaneous resolution of his symptoms.

In sum, this is how things seem to stand. Without even a bare difference to point to in terms of effective relief of Smith's symptoms, and with no demonstrable disease process underlying those symptoms, Dr Jones is obliged to conclude that the three preparations on her desk—the pharmaceutical product SAS, the ''official'' placebo and the green-candied Swotties, are functionally equivalent.

The conditions of her continuing medical registration oblige her to confine her prescribing to SAS or placebo; yet to prescribe either with any confidence (even at the 35% response level), she seems constrained to a measure of concealment. By vivid contrast, Swotties are what they all-too-obviously are, and hence can be supplied only in a transparent manner—unlike ''official'' placebo, which remains blinded by definition, or SAS, whose placebo-equivalence would also seem to need blinding for there to be any point in prescribing it.

Hence Dr Jones's uncomfortable conclusion: paradoxically, in terms of transparent prescribing, Swotties seem preferable to either SAS or placebo. They are also safer than SAS; and they are better tolerated—because actively enjoyed—than either. In equivalent conditions of transparency,[iv] they are as effective as either. As things stand, she has little choice but to advise Mr Smith that in her view there is currently no medical treatment for his condition that can improve on the performance of Swotties.

If there is a flaw in the reaching of this conclusion, Dr Jones awaits its identification and demonstration by others. If there is not, then the absurdity that the conclusion discloses, in the context of the empirical dispensing of medicines lacking attributable therapeutic benefit, seems uncomfortably persistent.

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REFERENCES

1 **Thompson WG**, Heaton KW, Smyth GT, *et al*. Irritable bowel syndrome in general practice: prevalence, characteristics and referral. *Gut* 2000;**46**:78–82.
2 **Ponyard T**, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2001;**15**:355–61.
3 **Lesbros-Pantoflickova D**, Michetti P, Fried M, *et al*. Meta-analysis: the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;**20**:1253–69.
4 **Talley NJ**. Evaluation of drug treatment in irritable bowel syndrome. *Br J Clin Pharmacol* 2003;**56**:362–9.
5 **Talley NJ**, Spiller R. Irritable bowel syndrome: a little understood organic bowel disease? *Lancet* 2002;**360**:555–64.
6 **Longstreth GF**, Thompson WG, Chey WD, *et al*. Functional bowel disorders. *Gastroenterology* 2006;**130**:1480–91.
7 **Drossman DA**. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006;**130**:1377–90.
8 **Muller-Lissner S**, Bollani S, Brummer R-J, *et al*. Epidemiological aspects of irritable bowel syndrome in Europe and North America. *Digestion* 2001;**64**:200–5.